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| EXAMINER | |
|---|---|
| DAVIS, MINH TAM B | |

| ART UNIT | PAPER NUMBER |
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| 1642 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

efiling@cojk.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/016,737 | MURPHY ET AL. | |
| | Examiner | Art Unit | |
| | MINH-TAM DAVIS | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *16 February 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *23-37* is/are pending in the application.

4a) Of the above claim(s) *25, 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23,24,26 and 28-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

***DETAILED ACTION***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/16/10 has been entered.

**Claims 23, 24, 26, and 28-37 are being examined.**

## *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

**1.** Claims 23, 31-32, 33-37 remain rejected under 35 USC 103(a) as being obvious over Sallusto et al, 1994 (J Exp Med, 179: 1109-1118, of record), in view of Bigotti G et al, 1991 (Prostate, V19, N1, p.73-87), as evidenced by Inaba K et al, 1987 (Journal of experimental medicine (UNITED STATES), 166 (1) p:182-94, of record), for reasons already of record in paper of 1/9/09.

The response asserts as follows:

Applicants must again strongly disagree with the Examiner rejection of claims 23, 31, 32, and 33-37. In particular, Bigotti et al. do not in any way disclose or suggest that the Langerhans cells characterized by binding of anti-S 100 polyclonal sera have taken in or begun processing any antigen, much less a prostate specific or prostate tumor associated antigen. It is well known to the artisan of ordinary skill that Langerhans cells are immature antigen presenting cells. In addition, it is well known to the skilled artisan and admitted by the Examiner that immature antigen presenting cells, such as Langerhans cells and immature dendritic cells, once they uptake antigen migrate to a lymph node and that during migration or shortly after arriving at a lymph node become a fully09 mature antigen presenting cell. It was also well known to an artisan of ordinary skill at the time of the present invention that Langerhans cells also could be induced to migrate to a lymph node when contacted with a inflammatory cytokine and that prostate carcinoma typically secrete inflammatory cytokines.

Bigotti et al as interpreted by the Examiner must be construed to teach the skilled artisan that Langerhans cells in low-grade prostate carcinoma are exposed to, and capture the antigen and have the ability to present the antigen to T cells. In addition, the Examiner asserts that the Langerhans cells are combining with HLA class II expressing prostate epithelial cells to induce prostate specific cytotoxic T cells and macrophage. As above, and in Applicants prior responses Bigotti et al. does not teach the artisan of ordinary skill that the Langerhans cells present antigen in low-grade prostate carcinoma. But merely teach that the presence of immature antigen presenting cells, for example, Langerhans cells, is a diagnostic indicator of a good prognosis in low-grade prostate carcinoma. The artisan of ordinary skill at the time of the present invention was well aware of the various issues regarding the immune reaction and surveillance of tumors.

It was well known that many tumors, including prostate tumors, produced IL-10 and other cytokines that down regulated the immune response directed against the tumor. See, for example, Sharma et al. and other references provided by Applicants.

Further, the Examiner has asserted that the Langerhans cells of Bigotti et al. must display a prostate antigen because the immune response, i.e., cytotoxic T cell expansion and the antibody response, are specific to membrane bound prostate tumor antigen in view of the teachings of the abstract and on pages 74 and 85 ofBigotti et al. The abstract of Bigotti et al. merely states Langerhans cell number is inversely correlated to the histopathological grane and directly to the expression of HLA class II-DR molecules by tumor cells and that the authors believe that this could be important in understanding the more favorable biological behavior of low-grade prostate carcinomas since Langerhans cells and HLA class II molecules may provide a means of eliciting the immune response. These characteristics are known activities of Langerhans cells and HLA class II molecules on whatever cells they appear. There is no suggestion here that the Langerhans cells actually found in the prostate are in the process of taking up prostate antigen or that the cells are in the process of presenting antigen to macrophage in the prostate of low grade prostate carcinoma. As above, and in Applicants prior responses, Langerhans cells are immature antigen presenting cells and must migrate to a lymph node to mature and contact with T cells to produce a cytotoxic T cell response. In addition, also as above and in Applicants prior responses, Bigotti et al. did not detect infiltrating lymphocytes which might indicate that antigen presenting cells might have successfully taken up and processed prostate antigen for presentation to naive T cells which would return to the prostate tumor if tumor infiltrating lymphocytes. Further as

above, carcinomas, including prostate carcinomas, where known to have an immunosuppressive environment and it was well known that Langerhans cells were present in normal prostate.

The response has been considered but is not found to be persuasive for the following reasons:

The response does not have any objective evidence showing that Langerhans cells (LCs) stained with anti-S-100 antibody, some of them are directly in contact with prostate tumor glands, and most of them are adjacent to the prostate tumor glands, as taught by Bigotti et al (Bigotti et al, p.76, first paragraph, p.79, last paragraph, bridging p.80) are immature antigen presenting cells. It is noted that in the presence of antigen, immature antigen presenting cells are capable of pick up and process in the antigen (Sallusto et al, p.1109, first column, first paragraph). Further, it is well known in the art that necrotic cancer cells shed cancer antigens into their vicinity and circulation. Applicant does not have any objective evidence that Langerhans cells at the vicinity of prostate cancer glands did not pick up the antigen during their journey from the skin or epidermis to the vicinity of prostate cancer glands.

Further, although Bigotti et al do not directly teach that Langerhans cells in the vicinity of prostate cancer cells capture prostate cancer antigen, and present prostate cancer antigen to T cells, Bigotti et al teach that:

1) The presence of Langerhans cells and HLA class II molecules **correlates** with low grade prostate cancers, as compared to high grade prostate cancers (first paragraph, and first two lines of second paragraph of the abstract, and first two lines of the paragraph under Conclusion on page 85), and

2) Such correlation is understandable in view that: a) Langerhans cells and HLA class II molecules **elicit the immune response,** capable of direct antigen presentation to immune cells, b) **Langerhans cells act as antigen presenting cells in neoplastic environment**, and c) HLA class II molecules expressed by neoplastic glandular epithelium, with the **aid of Langerhans** cells, interact with macrophages and with T helper lymphocytes, and cause expansion of cytotoxic T cells and enhancement of antibody response to **membrane-bound tumor associated antigen** (abstract, second paragraph, $4^{th}$-$7^{th}$ lines, and paragraph under Conclusion on page 85).

Such suggestion by Bigotti et al that Langerhans cells, being antigen presenting cells and eliciting the immune response, could contribute to controlling cancer growth in prostate cancer clearly provides **motivation** for making DCs specific for prostate cancer antigen in vitro, using the method of making dendritic cells taught by Sallusto et al, and replacing the model antigen tetanus toxin taught by Sallusto et al with prostate antigen, for use in inducing an anti-tumor immune response for treating prostate cancer.

Further, concerning the arguments that many tumors, including prostate tumors, secrete IL-10 and other cytokines that down regulate the immune response against tumor, as taught by Sharma et al and Steinbrink et al, previously submitted in the response, one cannot predict the effect of IL-10 on the response of the immune response in low grade prostate cancer, in view of the teaching of Steinbrink et al, submitted in the previous response. As taught by Steinbrink et al, the effect of IL-10 on T cell response in cancers, whether suppression or stimulating the immune response, depends on the types of tumor (p.1640, second column, third and fourth paragraph).

Concerning the argument that Bigotti et al. did not detect infiltrating lymphocytes which might indicate that antigen presenting cells might have successfully taken up and processed

prostate antigen for presentation to naive T cells which would return to the prostate tumor as tumor infiltrating lymphocytes, Applicant does not have any objective evidence or references showing that activated CD4+ T cells and CD8+T cells and activated B cells producing antibodies have to be present right at the site of the prostate cancer glands. One would have expected that the dendritic cells prepared in vitro as taught by the combined art would successfully present the prostate cancer antigen and activate T cells, in view of the teaching of Sallusto et al that cultured DCs are most efficient for presentation of antigens, and cause proliferation of T cells (Sallusto et al, figure 4 on p.1114), and further in view that it is the properties of DCs to activate CD4+ T cells and CD8+ T cells, as taught by Inaba et al.

Further, concerning the arguments that it was well known that Langerhans cells were present in normal prostate, the response has not provided any objective evidence that Langerhans cells are activated and presents normal prostate antigen in normal prostate environment. Bigotti et al teach that Langerhans cells act as antigen presenting cells in **neoplastic** environment (Bigotti et al, paragraph under Conclusion on page 85).

The response further asserts as follows:

The Examiner has noted that Troyer et al. did detect activated antigen presenting cells in prostate carcinoma samples. Troyer et al. defined these activated cells as dendritic cells, while the Examiner asserted that the activated antigen presenting cells were Langerhans cells. Based on this incorrect assertion the Examiner has concluded that Troyer et al. supports the conclusion of Bigotti et al. that it is well known in the art that activated Langerhans cells are Langerhans cells that are exposed to, and capture prostate antigen and has the ability to present the antigen to T

cells. To the contrary, Troyer et al. teaches that there are a few activated dendritic cells in prostatic carcinoma, not Langerhans cells. There is also no support in Troyer et al. that the Langerhans cells detected in prostate low-grade prostate carcinoma by Bigotti et al. have been exposed to and have taken up, processed and are presenting prostate specific antigen. As admitted above by the Examiner, the Langerhans cells are immature antigen presenting cells that must mature while migrating to a lymph node where presentation of whatever antigen would take place. As such, Applicants do not agree with the Examiner's combination of the cited references and there would be no prima facie reason to combine Bigotti et al. with Sallusto et al. to stimulate the proliferation response of T cells specific for any prostate antigen.

The response has been considered but is not found to be persuasive for the following reasons:

The response misrepresents the Examiner reasons. The Examiner did not state that Langerhans cells (LCs) stained with anti-S-100 antibody, some of them are directly in contact with prostate tumor glands, and most of them are adjacent to the prostate tumor glands, as taught by Bigotti et al (Bigotti et al, p.79, last paragraph, bridging p.80) are immature antigen presenting cells. The response does not have any objective evidence showing that Langerhans cells (LCs) stained with anti-S-100 antibody, some of them are directly in contact with prostate tumor glands, and most of them are adjacent to the prostate tumor glands, as taught by Bigotti et al (Bigotti et al, p.79, last paragraph, bridging p.80) are immature antigen presenting cells, supra.

Further, the prostate cancers taught by Troy et al are high grade prostate cancers, having Gleasons score of 4-8 (Troy et al, 1998, J Urology, 160: 214-219, especially p.215, first column,

item under Tissue sample). It is noted that Bigotti et al did not find Langerhans cells in high grade prostate cancer, such as grades 4 and 5.

**2.** Claim 24 remains rejected under 35 USC 103(a) as being obvious over Sallusto et al, in view of Bigotti G et al, and as evidenced by Inaba et al, supra, and further in view of Cohen, PA et al, 1994 (Cancer Research, 54(4): 1055-8) for reasons already of record in paper of 1/9/09.

The response asserts as follows:

As above, the combination of Sallusto et aL and Bigotti et al. fail to teach the compositions of the present invention. Instead, Bigotti et al. teach that macrophage likely induce the immune response seen in prostate cancer and that the presence of Langerhans cells can be used to stage prostate cancer tissue. As such, any combination with Inaba et al. and/or Cohen et al. can not provide the skilled artisan with incentive to combine the references to use a lysate of prostate cancer cells from a prostate cancer patient to make the compositions of the claim 24.

The response has been considered but is not found to be persuasive for the following reasons:

The combination of the teaching of Sallusto et al, Bigotti et al and Inaba et al suggests the composition of the claimed invention, supra.

It would have been obvious to use as prostate antigen, a lysate of prostate cancer cells from a prostate cancer patient, because prostate cancer cells would have several prostate cancer-specific antigens, and because a tumor lysate successfully primes the dendritic cells for inducing antigen-specific proliferation of antitumor CD4+ T cells, as taught by Cohen et al, and further

because using tumor lysate would be more convenient, and does not require the extra step of purification of the antigen.

**3.** Claim 26 remain rejected under 35 USC 103(a) as being obvious by Sallusto et al, in view of Bigotti et al, and as evidenced by Inaba et al, supra, as applied to claim 23, and further in view of Lutz et al (of record), for reasons already of record in paper of 1/9/09.

The response asserts as follows:

As above, the Sallusto et al., Bigotti et al., and/or Inaba et al. when considered either alone or in combination do not teach the compositions of the present invention. As such, the addition of Lutz et al. allegedly teaching immortalization of dendritic cells can not provide the skilled artisan with the motivation or guidance to make the composition as set forth in claim 26.

The response has been considered but is not found to be persuasive for the following reasons:

The combination of the teaching of Sallusto et al, Bigotti et al and Inaba et al suggests the composition of the claimed invention, supra.

It would have been *prima facia* obvious to a person of ordinary skill in the art at the time the invention was made to immortalize the dendritic cells taught by Sallusto et al, Bigotti et al, and Inaba et al, using the immortalizing method taught by Luz et al, because immortalizing dendritic cells would enable maintainance of dendritic cells *in vitro* for long periods of time, as taught by Luz et al.

**4.** Claims 28-29 remain rejected under 35 USC 103 as being obvious by Sallusto et al, Bigotti et al, Inaba et al, and Cohen et al, supra, as applied to claim 23, and further in view of Taylor et al (of record), for reasons already of record in paper of 1/9/09.

The response asserts as follows:

Applicants must again disagree with the reasoning of the Examiner. In particular, as above, Sallusto et al., Bigotti et al., and Inaba et al., do not teach the compositions of the present invention. Taylor et al. is directed to cryopreservation techniques and does not address the teachings of Bigotti et al. Bigotti et al. teaches that the immune response is likely induced in prostate cancer by macrophage. As such, Sallusto et al., Bigotti et al. and Inaba et al., when considered individually or in any combination does not teach or suggest the composition as set forth in claims 28 and 29.

The response has been considered but is not found to be persuasive for the following reasons:

The combination of the teaching of Sallusto et al, Bigotti et al, and Inaba et al suggests the composition of the claimed invention, supra.

It would have been *prima facia* obvious to a person of ordinary skill in the art at the time the invention was made to cryopreserve the dendritic cells taught by Sallusto et al, Bigotti et al, Stites, and Cohen et al, using the cryopreservation method taught by Taylor et al, to preserve the previously isolated dendritic cells for later use.

**5.** Claim 30 remains is rejected under 35 USC 103 as being obvious by by Sallusto et al, Bigotti et al, and Inaba et al, supra, as applied to claim 23, and further in view of Taylor et al (of

record), as applied to claim 28, and Lutz et al, of record, for reasons already of record in paper of 1/9/09.

The response asserts as follows:

Applicants must again disagree with the rejection of the Examiner, as above, the teachings of Sallusto et al., Bigotti et al., Inaba et al., and Taylor et al. do not disclose or suggest the compositions of the present application. The teachings of Lutz et al. when considered either alone or in combination with any of the other cited references does not cure the deficiencies of the primary references, Sallusto et al. and Bigotti et al. in that Bigotti et al. teaches away from the compositions of the present claims.

The response has been considered but is not found to be persuasive for the following reasons:

The combination of Sallusto et al, Bigotti et al, Inaba et al, and Taylor et al suggests the composition of the claimed invention, supra.

It would have been *prima facia* obvious to a person of ordinary skill in the art at the time the invention was made to immortalize the cryopreserved dendritic cells taught by Sallusto et al, Bigotti et al, Inaba et al and Taylor et al, using the immortalizing method taught by Luz et al, because immortalizing dendritic cells would allow maintainance of dendritic cells *in vitro* for long periods of time, as taught by Luz et al.

**Summary**

The response asserts as follows:

In view of the above remarks, Applicants respectfully request the Examiner to reconsider and withdraw the various rejections of claims 23, 24, 26, and 28-37 under 35 U.S.C. § 103(a) as being obvious over Sallusto et al., Bigotti et al. as evidenced by Inaba et al., in view of Stites, and Cohen et al., alone and in various combinations. In particular, Bigotti et al. teaches away from the compositions of the present invention by teaching that the immune response to prostate cancer is likely induced by macrophage and that Bigotti et al. teach no more than a method for staging prostate tumor samples. In light of the teachings of Bigotti et al. the skilled artisan would not have been motivated to produce the compositions of the present claims.

The response has been considered but is not found to be persuasive for the following reasons:

The claimed invention is obvious over the cited art, supra.

Further, contrary to the response assertion, Bigotti et al do not teach away from the claimed invention. Bigotti provide **motivation** for making DCs in vitro, using the method taught by Salllusto, because of the following teaching by Bigotti et al:

1) The presence of Langerhans cells and HLA class II molecules **correlates** with low grade prostate cancers, as compared to high grade prostate cancers (first paragraph, and first two lines of second paragraph of the abstract, and first two lines of the paragraph under Conclusion on page 85), and

2) This correlation with low grade prostate cancer is understandable, in view that: a) both Langerhans cells and HLA class II molecules **elicit the immune response,** capable of direct antigen presentation to immune cells, b) **Langerhans cells act as antigen presenting cells in neoplastic environment**, and c) HLA class II molecules expressed by neoplastic glandular

epithelium, with the **aid of Langerhans cells,** interact with macrophages and T helper lymphocytes, and cause expansion of cytotoxic T cells and enhancement of antibody response to **membrane-bound tumor associated antigen** (abstract, second paragraph, $4^{th}$-$7^{th}$ lines, and paragraph under Conclusion on page 85).

Further, the teaching of Bigotti et al that macrophages play a primary role in controlling prostate tumor progression, but Langerhans cells, as antigen presenting cells, elicit the immune response, and aiding in the expansion of cytotoxic T cells and enhancement of antibody response to membrane-bound tumor associated antigen, actually provide motivation for making antigen presenting cells, such as dendritic cells, in vitro, as taught by the combined art, for potential treatment of prostate cancer patients, to complement the action of macrophages, and further enhancing the immune response to tumor antigen in prostate cancer patients.

## *Conclusion*

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, MISOOK YU can be reached on 571-272-0839. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MINH TAM DAVIS
August 10, 2010

/MISOOK YU/
Supervisory Patent Examiner, Art Unit 1642